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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,830	05/17/2006	Leifeng Cheng	056291-5286	5753

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EXAMINER	
WILLIS, DOUGLAS M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,830	CHENG, LEIFENG	
	Examiner	Art Unit	
	DOUGLAS M. WILLIS	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7 and 8* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-17-06; 09-22-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

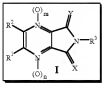
DETAILED ACTION

Status of the Claims / Priority

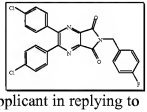
Claims 1-3, 5, 7 and 8 are pending in the current application. According to the *In The Claims*, filed September 22, 2008, claims 1-3, 5, 7 and 8 were amended and claims 4 and 6 were cancelled. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/GB2004/04934, filed November 24, 2004, which claims priority under 35 U.S.C. § 119(a-d) to GB 0327331.5, filed November 25, 2003.

Restrictions / Election of Species

Applicant's provisional election of the following, with traverse, in the reply filed on



September 22, 2008, is acknowledged: a) Group I - claims 1-3 and 5; and b) substituted pyrrolopyrazine of formula I - p. 19, example 1, shown right below, and hereafter referred to as 2,3-bis(4-chlorophenyl)-6-(4-fluorobenzyl)-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione, where m = 0; n = 0; X = -O-; Y = -O-; R^1 = -Ph, optionally substituted with *p*-Cl; R^2 -Ph, optionally substituted with *p*-Cl; and R^3 = -Bn, optionally substituted with *p*-F ($PhC_{1-4}alkyl$). Claims 1-3 and 5 are readable upon the species. Affirmation of this election must be made by applicant in replying to this Office action.



The traversal is on the ground(s) that: a) the applicants fail to understand the rationale behind certain of the examiner's characterizations and reasoning; and b) the *Election of Species* requirement is inconsistent. This is found persuasive regarding the *Election of Species* requirement. Applicant will not be held non-responsive for groups not included in the

Requirement for Restriction as there are only 3 groups. However, the remainder of the traversal is not found persuasive because the multiple inventions in the instant application are independent or distinct for the reasons disclosed in the *Requirement for Restriction / Election of Species*, mailed on May 20, 2008. Furthermore, there would be a serious burden on the examiner if restriction was not required because the inventions have acquired a separate status in the art due to their divergent subject matter and would require a different field of search.

The requirement is still deemed proper and is therefore made FINAL.

The elected species above has been found to be free of the prior art. Thus, the examiner has expanded the forthcoming prosecution to include all claims relevant to the genus of Group I, and has selected as an alternative species, 3-(1,4-diazepan-1-yl)-5-(3-methyl-1*H*-indazol-5-yl)pyrazin-2-amine, shown to the right above, for a first Office action and prosecution on the merits.

Claims 7 and 8 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Thus, a first Office action on the merits of claims 1-3 and 5 is contained within.

Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR

DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art (including information disclosed under 37 CFR 1.97 and 1.98).
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825).

Specification - Disclosure

The disclosure is objected to because of the following informalities: the reaction schemes with respect to Step D on p. 18 and Step E on p. 19 are abridged on the right and require replacement. Appropriate correction is required.

Specification - Abstract

Applicant is reminded of the proper content of an abstract of the disclosure.

With regard particularly to chemical patents, for compounds or compositions, the general nature of the compound or composition should be given as well as the use thereof, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example, unless variations are necessary. See MPEP § 608.01(b), Section B.

The abstract of the disclosure is objected to because R^1 and R^2 should be amended to reflect the scope of the *Requirement for Restriction / Election of Species*, mailed on May 20,

2008. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 1 is objected to because of the following informalities: 1) a space is missing in the definition of R^3 as *a heteroaryl group* in line 6 of the claim; 2) the term *and* is missing after the semicolon in line 11 of the claim; and 3) there is an extra space between *of* and R^1 in line 12 of the claim. Appropriate correction is required.

Claim 2 is objected to because of the following informalities: 1) the term *salts* should be replaced with *salt* in line 3 of the claim; and 2) the term *and* is missing after the semicolon in line 11 of the claim. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Pyrazine-substituted indazoles and pharmaceutical compositions of the formula (1.0)

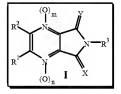
Claims 1 and 5 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where m = 0 and n = 0, does not reasonably provide enablement for substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. Substituted pyrrolopyrazines and pharmaceutical compositions of the formula

I, where $m \neq 0$ and $n \neq 0$, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and use substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, shown right;



(b) *Nature of the invention* - the nature of the invention is evaluation of substituted pyrrolopyrazines and pharmaceutical compositions of the formula I and the pharmacokinetic behavior of these substances in the human body as cb1 modulators;

(c) *State of the prior art* - *Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's

substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$ (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m = 0$ and $n = 0$; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$. The specification lacks working examples of substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant

is insufficiently enabled for making and using substituted pyrrolopyrazines and pharmaceutical compositions of the formula I, where $m \neq 0$ and $n \neq 0$, is clearly justified.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

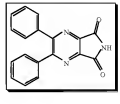
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsuda, et al. in *Agric, Biol. Chem.*, 45(9), **1981**, pp. 2129-2130, in view of Patani, et al. in *Chem. Rev.*, 96, **1996**, pp. 3147-3176.

The instant application recites substituted pyrrolopyrazines of the formula I, shown to the

left, where m = 0; n = 0; X = -O-; Y = -O-; R^1 = -Ph; R^2 -Ph; and R^3 = $-CH_3$ (C_{1-15}alkyl), as cb1 modulators.

Tsuda, et al. (*Agric, Biol. Chem.*, 45(9), **1981**) teaches the synthesis of substituted pyrrolopyrazines of the formula I, shown to the right, where m = 0; n = 0; X = -O-; Y = -O-; R^1 = -Ph; R^2 -Ph; and R^3 = -H [p. 2129,



Scheme 1, compound 6f].

Patani, et al. (*Chem. Rev.*, 96, **1996)** teaches the relationship between $-CH_3$ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity [p. 3148, column 1], via a direct adaptation of Grimm's Hydride Displacement Law [p. 3152, section A4; p. 3153, column 1, ¶ 2; p. 3153, Table 12, column 2].

The only difference between the applicant's instantly recited substituted pyrrolopyrazines of the formula I and Tsuda's substituted pyrrolopyrazines of the formula I is R^3 is $-CH_3$ in the instantly recited substituted pyrrolopyrazines of the formula I, whereas R^3 is -H in Tsuda's substituted pyrrolopyrazines of the formula I.

The MPEP § 2112.01, Section I states and the court recognizes that *where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness is established.* {*In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)}.

Consequently, since: a) Tsuda teaches substituted pyrrolopyrazines of the formula I, where R^3 is -H; b) Patani teaches the relationship between $-CH_3$ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity; and c) the MPEP § 2112.01, Section I states and the court recognizes that *where the claimed and prior art products are identical or substantially identical in structure, a prima facie case of obviousness is established*, one having ordinary skill in the art, at the time this invention was made, would have been motivated to combine the teachings of Tsuda and Patani and replace the -H atom at R^3 of Tsuda's substituted pyrrolopyrazines of the formula I, with a $-CH_3$ group, with a reasonable expectation

of success and similar therapeutic activity, rendering claims 1 and 2 obvious.

Allowable Subject Matter

Claim 3 is allowed.

The following is a statement of reasons for the indication of allowable subject matter:

The limitation(s) on the core of the substituted pyrrolopyrazines and pharmaceutical compositions of the formula I that are not taught or fairly suggested in the prior art is/are: 1) R^1 and R^2 is phenyl, optionally substituted with halo, etc. on the periphery of the dihydroimidazolone core; and 2) R^3 is $C_{3\text{-}15}$cycloalkyl, phenyl$C_{1\text{-}4}$alkyl, etc. on the periphery of the dihydroimidazolone core. These limitations are present in all of the recited species in claim 3.

Consequently, the species disclosed in claim 3 are neither anticipated nor obviated by the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624